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Lung Cancer in the Elderly—Important Considerations When Assessing Fitness for Treatment

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Abstract
Purpose of Review Lung cancer is increasingly a disease of the elderly. Historically, the information on how best to treat these patients is scant, but over recent years, there have been increasing data to support both systemic and targeted treatment as would be offered to younger patients. This paper aims to summarise the considerations behind this.
Recent Findings The introduction of a screening tool to help understand the overall health of patients will ensure that older cancer patients are considered for all active anti-cancer therapies. These geriatric assessment tools include several important domains such as nutrition, cognition, social support, comorbidities and performance status.

For those patients who may not be suitable for aggressive therapies such as surgical resection, lower morbid radical therapies such as SBRT or thermal ablation provides a useful alternative.
Summary It is clear that in previous years, the elderly patient with lung cancer did not receive treatment comparable to younger patients. In the advent of modern diagnostic and therapeutic modalities, however, this approach is no longer sustainable. With careful selection of patients and optimisation, the elderly patient can now be offered similar treatments to improve survival in an ageing population.

Keywords Lung cancer · Elderly · Geriatric assessment · Frailty

Background

Lung cancer is the most common malignancy and the most common cause of cancer death worldwide [1]. In the UK, it is the third most common cancer and accounted for 13% of all new cancer cases in 2015 and 22% of all cancer deaths. Five-year survival is poor at approximately 10% and this reduces to 6–7% in patients over the age of 80. These figures have changed little over the last 40 years [2], and this is partly because the majority of cases continue to be diagnosed at a late stage, with 72–76% of patients presenting with stage III or IV disease [3]. The burden of disease from lung cancer therefore remains significant and this is particularly true in the elderly population. Between 2013 and 2015, 44% of new lung cancer cases were in patients aged 75 and over with the highest incidence in the 80 to 89 age group, peaking at 589 cases per 100,000 for males and 339 cases per 100,000 for females [3].

In the UK over 40 years up to 2016, the proportion of the population considered elderly rose from 14.2 to 18%. This is projected to continue to rise to almost 25% by 2046 [4].

An ageing population is also seen worldwide and despite the demographics suggesting that the population is ageing, many older patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) do not receive chemotherapy. In a recent review, only 66% of adults over 65 years of age, with locally advanced NSCLC, received cancer treatment [5•].

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Surgical Treatment with Radical Intent

The British Thoracic Society (BTS), the European Respiratory Society in conjunction with the European Society of Thoracic Surgery (ERS/ESTS) and the American College of Chest Physicians (ACCP) all provide guidelines regarding the assessment of fitness for radical therapy in patients with lung cancer and in particular, NSCLC [6–8].

When considering treatment with radical intent, surgery is still considered the gold standard despite the recent increase in popularity of stereotactic radiotherapy (SBRT). Despite improving outcomes, this is because of a paucity of long-term follow-up data for those patients undergoing SBRT. Therefore, consideration of fitness for radical therapy primarily equates to fitness for either lobectomy or pneumonectomy [9].

The BTS guidelines (2010) recommend a tripartite risk assessment model considering operative mortality, perioperative myocardial risk and postoperative dyspnoea. Operative mortality is felt to be best risk assessed using the Thoracoscore model which takes into account age, gender, performance status, comorbidities, breathlessness and proposed procedure [10]. Perioperative myocardial risk assessment is necessary as the risk of cardiac death or myocardial infarction associated with lung resection is quoted as 1–5%. Therefore, a cardiology review for consideration of optimisation is recommended in patients with known active cardiac conditions, those with poor cardiac functional capacity and those with three or more risk factors. It is thought that no further investigations are required in those with fewer than two risk factors. Finally, lung function with particular focus on FEV_1 and DLCO is used to estimate operative mortality and postoperative dyspnoea with previous suggested cut-offs in the region of 40% predicted in both domains. Spirometry alone is not considered sufficient unless normal in the setting of good exercise tolerance given inaccuracies in predicting outcomes. Therefore, in patients considered moderate to high risk of postoperative dyspnoea, it is recommended that exercise testing should be performed. Options include 6-min walk test, shuttle walk test, stair climbing or formal cardiopulmonary exercise testing (CPET). Due to problems with composite end points and variable study methods, definitive predictive values are not possible; however, the guidelines suggest considering a shuttle walk of greater than 400 m or a peak oxygen consumption (VO_{2max}) of more than 15 ml/kg/min as an indication of adequate function [6].

The ERS/ESTS guidelines (2009) follow a broadly similar theme. In terms of lung function however, the threshold for exercise testing is much lower with the recommendation that it should be performed in patients with either an FEV_1 or DLCO less than 80% predicted [7]. This recommendation has been further developed to suggest using predicted postoperative FEV_1 (ppo-FEV_1) and ppo-DLCO values of 60% predicted [11]. The most reliable and reproducible form of exercise testing is CPET. Using this technique, values less than 10 ml/kg/min exclude patients from radical therapy while it is possible to offer resection in those greater than 20 ml/kg/min. Split function studies including segment counting or more objective scintigraphy should then be performed in those borderline cases in order to determine fitness for resection. Predicted postoperative FEV_1 and ppo-DLCO can then be calculated with the suggestion that values of less than 30% predicted signify patients at high risk [7].

Recent retrospective data on 53 patients has confirmed safety of resection in patients with a preoperative FEV_1 or DLCO cutoff of 40%; however, the authors also suggested that with new operative techniques, it may be possible to push these boundaries further [12].

The ACCP guidelines (2013) use ppo-FEV_1 and ppo-DLCO as the discriminators in evaluating fitness for surgery; however, within these guidelines, the authors recommend a value of below 60% predicted as the point at which further investigations such as exercise testing are indicated. In concordance with the European guidelines, a value of less than 10 ml/kg/min is deemed to signify high risk precluding surgery [8].

Specific reference is made in the ACCP guidelines that age should not be used as a discriminating factor. Retrospective data from more than 1000 patients at that time suggested that patients over the age of 80 were less likely to undergo resection, largely due to comorbidities; however, those subjects who did undergo surgery had comparable survival [13]. More recently, further retrospective data from 88 patients confirmed, that in selected patients, perioperative mortality, morbidity and 5-year survival are all comparable to younger cohorts [14].

Retrospective data from 44 patients confirmed similar rates of perioperative mortality and postoperative complications but failed to replicate long-term survival comparability [15]. More recently, a retrospective analysis including 2186 patients who underwent radical resection for stage I NSCLC demonstrated that the 5-year lung cancer specific mortality increased with increasing age. Mortality was 7.5% in the under 65s, 10.7% in the 65–74 group and 13.2% in the over 75s [16].

The ERS/ESTS guidelines also make specific reference to the potential benefit of pre- or perioperative pulmonary rehabilitation programmes, suggesting that improvements in functional status may improve outcomes but caution that further research is required [7]. A subsequent randomised controlled trial comparing usual care with an early postoperative exercise intervention programme failed to demonstrate improvements in 6-min walk test or quality of life [17].

Preoperative programmes have resulted in more favourable results. A recent retrospective case series assessing the impact of a preoperative pulmonary rehabilitation programme specifically for elderly patients suggested improvements in FEV_1, DLCO and VO_{2max} resulting in good surgical outcomes [18]. These findings are a little out of keeping with known data on pulmonary rehabilitation which demonstrates improvements in functional status, quality of life and dyspnoea scores without altering lung function [19, 20]; however, this would appear to reflect the findings from an earlier randomised controlled trial involving 40 patients. There was a statistically significant difference in VO_{2max} between those who underwent preoperative pulmonary rehabilitation and those who did not; however, this was not reflected in lung function values such as FEV_1 or DLCO and was also not reflected in patient-centred outcomes such as the BORG dyspnoea scale. No comment was made in this study about either surgical outcomes or postoperative complications [21].

Non-surgical Treatment with Radical Intent

Radical radiotherapy is the treatment of choice in patients in whom the risk of surgery is unacceptable. The ERS/ESTS guidelines suggest that the lower limits of respiratory function to determine safety in radical radiotherapy or chemotherapy have not been defined and so therefore do not make specific recommendations [7]. This is echoed by the BTS who suggest that decisions should be made by clinical oncologists taking into account performance status and comorbidities [6].

Initial data on radical radiotherapy in the form of Stereotactic Body Radiation Therapy (SBRT) has shown control of local disease in between 80 and 98% with overall survival of 50–70% at 3 years. It has been shown to be well tolerated with low toxicity allowing elderly patients and those with significant comorbidities to undergo potentially curative treatment when this would not previously have been the case, and elderly patients seem to have comparable rates of control, toxicity and tolerability following SBRT as compared with younger patients [22]. Further pooled analysis of 58 patients suggested an overall survival at 3 years of 95% with recurrence-free survival of 86% [23] and a meta-analysis of 7869 patients demonstrated overall survival at 3 years of 89% and disease-free survival of 73% [24].

The suggestion from recent studies therefore is that SBRT in elderly patents is a tolerable and effective treatment, and can be used in those who are not suitable for resection or non-surgical radical therapies such as concurrent chemoradiotherapy [25•]. A recent publication from the American Society of Radiation Oncology (ASTRO) presents the evidence-based guidelines on SBRT in lung cancer [26]. This guidance acknowledges that, whilst histological proof of cancer should be sought prior to SBRT, in certain circumstances, the risks of biopsy are precluded—in the elderly, this is primarily due to cardio-respiratory disease. The guidelines therefore provide consensus that SBRT can be delivered in these patients without histological proof, as long as the patients have been discussed in a multidisciplinary manner with agreement that lesions are radiographically and clinically consistent with a malignancy. This, in turn, may enable SBRT in an elderly comorbid cohort who would otherwise not be suitable for other radical-intent treatments.

Treatment with Non-radical Intent

Of the NSCLC patients, 25–30% present with locally advanced disease at diagnosis [27] and chemoradiotherapy is the recognised standard treatment in patients with good performance status [28], with a recent meta-analysis suggesting this is also applicable to the elderly population [29]. Advancing age is often considered to be a factor influencing tolerance of oncological intervention and as such is used as a determining factor in treatment decisions [30]; however, a systematic review found similar efficacy and safety for elderly patients receiving chemotherapy for colorectal cancer when compared with younger patients when adjusted for other factors such as comorbid history or performance status [31].

A recent meta-analysis demonstrated elderly patients receiving concurrent chemoradiotherapy had a statistically significant shorter overall survival of almost 4 months when compared with their younger counterparts [32]; however, a subsequent prospective study from Spain demonstrated that comprehensive geriatric assessment identified elderly patients who were suitable for concurrent chemoradiotherapy with survival and toxicity outcomes comparable with younger subjects [33•].

Furthermore, the Japanese Oncology Group showed that the overall median survival for combined chemotherapy and radiotherapy was higher than that for radiotherapy alone in unresectable stage III NSCLC.

These data would suggest a justification for chemotherapy—either alone or as a combined modality—in the elderly. However, there is a well-documented adverse event profile and decisions to treat must be taken on a case by case basis.

Specific Geriatric Considerations

FEV_1 is known to decline with age, independent of cardiovascular disease. It is also known that the variability of spirometric measurements increases with advancing age [34]. As a result, FEV_1 is likely to be a less reliable risk stratification tool in the elderly population.

It is also known that VO_{2max} declines with age, but the utilisation in preoperative risk stratification appears to be justified given that the correlation with postoperative outcomes and complications is much more robust and is consistent even amongst the elderly [35].

The ECOG performance status is well established as a prognostic indicator in lung cancer, but the ability to successfully treat an elderly patient also depends on other factors. The International Society of Geriatric Oncology (SIOG) recognised the heterogeneity of the elderly population, particularly with reference to physiological reserves and geriatric impairments not always reflected in the inferred performance status. As such, the SIOG taskforce recommended the introduction of geriatric assessments (GA) prior to confirming treatment decisions. A systematic review demonstrated that the prevalence of geriatric impairments, such as changes in cognitive function, nutritional status, activities of daily living, frailty and physical capacity was high even in patients with good ECOG performance status and that this had a consistent correlation with mortality. The geriatric assessment therefore leads to changes in management, often downgrading treatment plans to less aggressive regimens [36]. This finding was confirmed in a prospective observational cohort study from the Netherlands in 2017 which included 83 patients. Seventy-eight percent were found to have geriatric impairments and 58% of these were previously undiagnosed. This resulted in a change of treatment in 34% of the patients [37].

Other Novel Treatments

Proton beam therapy is a novel treatment in which a more concentrated dose of radiation is administered, lowering the dose delivered to normal tissues. This reduced toxicity is particularly relevant to an elderly population with increased comorbidities. One retrospective analysis demonstrated a 3-year overall survival of 67% but with lower rates of pneumonitis when compared to SBRT [38].

Radiofrequency and microwave thermal ablation are other treatment options in patients who are unfit for resection, although there is an increase in local failure rates with progression in 31–42% with an overall 3-year survival of 36–88%. The complication rate is higher than other novel treatments however with a pneumothorax rate of up to 63% [39]. This is corroborated by a recent retrospective study of 134 patients demonstrating a 2-year overall survival of 71% and 2-year local control rate of 51% [40].

One retrospective study of 84 patients recently demonstrated unsurprisingly poorer outcomes in elderly patients when compared to resection but with relative safety suggesting that this should be considered as an alternative treatment option [41].

Conclusion

Assessing fitness for treatment in lung cancer remains difficult in all age groups. Guidelines suggest initial screening using either current or postoperative predictive lung function values such as FEV_1 and DLCO before conducting exercising testing in those at high risk. Various methods are available, of which the most reliable and reproducible is formal cardiopulmonary exercise testing (CPET). Subsequently, in thoracic surgery, the most validated parameter with best correlation to outcomes is VO_{2max}.

Elderly patients appear to have similar outcomes with many treatment modalities when compared to younger counterparts if adjusted for other factors such as comorbidities, of which there is however a clearly higher prevalence. This would therefore suggest that treatment decisions should not be defined solely on the basis of age, but include comprehensive geriatric assessments in the determination of a patient's fitness prior to ratification of management decisions, especially given the heterogeneity within the elderly population. This approach has placed a focus on the treatment of cancer in older adults, with the individualisation of their treatments based on their overall health assessments. Over the last 5 years, the promotion of Geriatric Oncology has become widespread both in the UK (BGS Oncogeriatrics) and abroad (SIOG—International Society of Geriatric Oncology) with a view to the optimisation of oncological management of the elderly population.

Compliance with Ethical Standards

Conflict of Interest D.J. McCracken and A.J. Moore declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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